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09/589,870	06/05/2000	Stephen C. Goshorn	690022.547	1301

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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/589,870	GOSHORN ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-39 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-39 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed February 7, 2002 in Paper No. 14 is acknowledged and has been entered. Claims 1-17, 40-64, and 66 have been canceled. Claims 18, 21-24, 26, 32-34, 38, and 39 have been amended.

2. Claims 18-39 and 65 are pending in the application and are currently under prosecution.

Election/Restrictions

3. Applicants affirmed the election with traverse of group II in Paper No. 14. Because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Nevertheless, Applicants have canceled claims drawn to non-elected inventions in Paper No. 14.

Specification

4. In the Office Action mailed June 22, 2001 (Paper No. 8), the specification was objected because of the improper use of the trademark Primatized™. In reply Applicants have amended the specification to correct the impropriety, thus obviating the ground of the objection. Accordingly, the objection to the specification is withdrawn.

Claim Objections

5. In the Office Action mailed June 22, 2001 (Paper No. 8), claim 32 was objected to because the claim recited the limitation "the linker comprises at least four Gly_4Ser linkers". As the recitation contains an amino acid sequence of more than four amino acid residues, namely GGGGS, the claim contained sequence disclosures encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). In reply, Applicants have amended claim 32 and submitted paper and computer-readable copies of a substitute Sequence Listing to

comply with the requirements of 37 CFR § 1.821-1.825, thus obviating the ground of the objection. Accordingly, the objection to claim 32 is withdrawn.

Grounds of Claim Rejections Withdrawn

6. In the Office Action mailed June 22, 2001 (Paper No. 8), claims 18-39 and 65 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 18-39 and 65 were stated to be indefinite because claims 18, 24, 38, and 39 recited the phrase "streptavidin, Figure 4". Recitation of the phrase rendered the claims indefinite because it was immediately apparent to which sequence in the figure the claim referred, and furthermore, because the numbering system used in the figure is confusing. In reply, Applicants have amended claims 18, 24, 38, and 39 to recite the phrase "as set forth in SEQ ID NO: 2" following "streptavidin". Therefore, it is presently clear that the claims refer to the amino acid sequence of streptavidin, which is set forth in SEQ ID NO: 2. Accordingly, this ground of rejection is withdrawn.

(b) Claims 18-39 and 65 were stated to be indefinite because claim 18 recited the phrase "a first and a second polypeptide joined end to end". As set forth in the Office Action mailed June 22, 2001, the use of the phrase rendered the claim indefinite because it was unclear whether the terms first polypeptide and second polypeptide were meant to indicate the amino-terminal polypeptide and the carboxyl-terminal peptide, respectively, or were merely meant to distinguish one from the other; and the fact that the first and second polypeptides are joined end to end is not limiting with regard to the orientation of the polypeptides relative to one another within the fusion protein. In reply, Applicants have traversed this ground of rejection, arguing that one skilled in the art would understand that the phrase is merely meant to distinguish one polypeptide from the other and not meant to be limiting with regard to the orientation of the polypeptides relative to one another within the fusion polypeptide. This argument is not persuasive, since claim 18 is rendered indefinite by recitation of the phrase for the reasons stated in the Office Action mailed June 22, 2001. Nevertheless, Applicants'

remarks carry an implied assurance that Applicants intend the terms "first polypeptide" and "second polypeptide" to merely distinguish one polypeptide from the other, and without limiting the first polypeptide to the N-terminus of the fusion protein, or the second polypeptide to the C-terminus. Therefore, this ground of rejection is withdrawn.

(c) Claims 18-39 and 65 were stated to be vague and indefinite because claim 18 recited the phrase "functional variant". The use of the phrase rendered the claim vague and indefinite because it could not be ascertained what constituted a functional variant of streptavidin. In reply Applicants have amended claim 18 to recite a limitation requiring the "functional variants" to comprise an amino acid sequence that is at least 90% identical to the amino acid sequence set forth in native sequence of streptavidin, i.e., SEQ ID NO: 2. Furthermore, Applicants have amended claim 18 to recite a limitation requiring the "functional variants" to retain the ability to bind biotin. Accordingly, the amendment to claim 18 has rendered this ground of rejection moot, since claim 18 presently defines the term "functional variant" as any polypeptide comprising an amino acid sequence that is at least 90% identical to the amino acid sequence set forth in SEQ ID NO: 2 that although differing in amino acid sequence from SEQ ID NO: 2, retains the ability of the polypeptide of SEQ ID NO: 2 to bind biotin. Therefore, this ground of rejection is withdrawn.

(d) Claim 21, 22, and 65 were stated to be indefinite because claim 21 recited the phrase "between four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, and twenty amino acids". The phrase rendered the claim indefinite because it was unclear whether the phrase was meant to recite a range or ranges of values, and moreover, it was unclear what the values of the limits of the range or ranges were and whether the range were intended to include values of less than whole integers. In reply, Applicants have amended claim 21 to obviate this basis of rejection; therefore, this ground of rejection is withdrawn.

(e) Claim 22 was stated to be indefinite because the claim recited the phrase "wherein the linker is between five to ten". The use of the phrase rendered the claim indefinite because it was unclear whether the limitation requires the linker to consist of a number of amino acids between 5 and 10 or a number of amino acids ranging from 6 to

10. In reply, Applicants have amended claim 22 to obviate this basis of rejection; therefore, this ground of rejection is withdrawn.

(f) Claim 23-37 and 65 were stated to be vague and indefinite because claim 23 recited the phrase "a fragment thereof". The use of the phrase rendered the claim vague and indefinite because it could not be ascertained whether the claim required the fragment to specifically bind the antigen to which the antibody specifically binds. In reply, Applicants have amended claim 23 to obviate this basis of rejection; therefore, this ground of rejection is withdrawn.

(g) Claims 26-37 were stated to be indefinite because claim 26 recited the phrase "scFv" in parentheses. The use of the phrase in parentheses rendered the claim indefinite because it was unclear whether the phrase was intended to be a limitation or merely parenthetical in nature. In reply, Applicants have amended claim 26 to obviate this basis of rejection; therefore, this ground of rejection is withdrawn.

(h) Claims 33-37 were stated to be vague and indefinite because claim 33 recited the phrase "is specific for a cell surface protein or a cell-associated stromal or matrix protein". The use of the phrase rendered the claim vague and indefinite because it was not clear whether the antibody was required to specifically bind a cell surface protein or a cell-associated stromal or matrix protein. In reply, Applicants have amended claim 33 to obviate this basis of rejection; therefore, this ground of rejection is withdrawn.

(i) Claim 34 was stated to be indefinite because of the use of the trademark "Primatized™". In reply, Applicants have amended claim 34 to obviate this basis of rejection; therefore, this ground of rejection is withdrawn.

Claims Rejections Maintained and Response to Applicants' Remarks

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 18-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the single-chain antibody-streptavidin fusion proteins huNR-LU-10 scFvSA and B9E9 scFvSA, does not reasonably provide enablement for any other fusion protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in the Office Action mailed June 22, 2001 (Paper No. 8).

As noted in the Office Action mailed June 22, 2001, the breadth of the claims encompasses a fusion protein comprising at least 129 amino acids of streptavidin and *any other polypeptide*. Furthermore, in terms of the single-chain antibody-streptavidin fusion protein, the claims encompass a fusion protein comprising a variable light chain and a variable heavy chain in any orientation and with any or no linker separating these two elements. The teachings of the specification, however, cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims and is insufficient in view of the state of the art and the level of unpredictability in the art, to enable the skilled artisan to make and use the invention with a reasonable expectation of success without needing to perform undue experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Applicants have traversed these grounds of rejection under 35 USC § 112, first paragraph, arguing to the contrary that the specification provides an enabling disclosure for the following reasons:

(a) The scientific literature provides examples of fusion proteins, which are not exemplified in the specification. In fact, Applicants contend that the claimed fusion proteins and methods for making and using such fusion proteins are "widely known in the art" (page 7, paragraph 3).

(b) The testing and screening required to make and use the claimed invention is "merely routine, rather than undue, experimentation" (page 8, paragraph 1).

(c) The utility of the claimed invention is widely known (page 8, paragraphs 2-4).

(d) The methods of using the disclosed invention do not necessitate any particular level of production (page 9, paragraph 1).

(e) The optimal length of a linker and the order of the variable subunits of the antibody are easily determined experimentally (page 9, paragraph 4).

Applicants' arguments have been carefully considered, but have not been found persuasive. First, Applicants are reminded that this rejection has been made because the enablement requirements of 35 USC § 112, first paragraph are not met by the disclosure; accordingly, Applicants' arguments pertaining to the utility of the invention are not particularly germane, since the claims were not rejected under 35 USC § 101 as lacking an asserted specific, substantial, and credible utility.

On the other hand, although the invention has a specific, substantial, and credible utility, for the reasons stated in the rejection, the disclosure does not provide sufficient guidance, direction, and exemplification to enable the skilled artisan to make the claimed invention, or to use the claimed invention as the specification asserts the invention can be used without need to perform undue experimentation. In other words, contrary to Applicants' stated opinion, in view of the preponderance of evidence, it is apparent that the skilled artisan given only the benefit of Applicants' disclosure, could not make and use the claimed invention with a reasonable expectation of success without the need to perform additional, undue experimentation. The particular reasons

that this is so have been set forth in the Office Action mailed June 22, 2001, and presently there is no factual evidence of record that serves to overcome the presently established case for lack of enablement. Therefore, the rejection of claims 18-39 under 35 USC § 112, first paragraph for the reasons set forth in the Office Action mailed June 22, 2001 (Paper No. 8) is maintained.

9. Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed June 22, 2001 (Paper No. 8).

Claim 65 is presently drawn to a pharmaceutical composition comprising a fusion protein according to any one of claims 18-39; however for the reasons stated in the Office Action mailed June 22, 2001, the teachings of the specification cannot be extrapolated to the enablement of the claims.

In reply to the Office Action, Applicants have traversed these grounds of rejection under 35 USC § 112, first paragraph, submitting that while therapeutic and diagnostic utility has been contemplated, the claimed invention can be used otherwise. Furthermore, without acquiescing to the basis of the rejection, Applicants state that claim 65 has been amended to recite "a composition" rather than "a pharmaceutical composition". Additionally, Applicants opine that the examples disclosed in the specification would enable the successful use of the claimed invention without need for further undue experimentation, and would require only further routine experimentation.

Applicants' traversal has been carefully considered; however, contrary to Applicants' opinion, in view of the preponderance of evidence, it is apparent that the teachings of the specification cannot be extrapolated to the enablement of claims drawn to a pharmaceutical composition in order to meet the requirements of 35 USC § 112, first paragraph. Since claim 65 has not been amended as Applicants have stated in their remarks, the rejection of claim 65 under 35 USC § 112, first paragraph for the reasons stated in the Office Action mailed June 22, 2001 is maintained.

10. Claims 18-22, 38, 39, and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons stated in the Office Action mailed June 22, 2001 (Paper No. 8).

As broadly written, the claims are drawn to an enormous genus of fusion proteins or pharmaceutical compositions comprising these fusion proteins. However, in this case, the written description only sets forth methods for producing two species of the fusion proteins, both of which are single-chain antibody-streptavidin fusion proteins. Therefore, the disclosure fails to meet the written description requirements of 35 USC § 112, first paragraph.

Applicants have traversed the grounds of rejection under 35 USC § 112, first paragraph, arguing that the disclosure provides a sufficient written description of a representative number of members of the genus of fusion proteins and pharmaceutical compositions to satisfy the requirements of 35 USC § 112, first paragraph.

Applicants' arguments have been carefully considered, but have not been found persuasive. The disclosure of two species of the fusion proteins, both of which are single-chain antibody-streptavidin fusion proteins, is not representative of the claimed genus of fusion proteins or pharmaceutical compositions comprising said fusion proteins, since the skilled artisan given only the benefit of Applicants' disclosure, could not immediately envision or recognize a reasonable number of the members of the claimed genus, nor would the skilled artisan be able to distinguish the members of the claimed genus from other fusion proteins or pharmaceutical compositions, which are not encompassed by the claims. For example, although presently claim 18 recites a limitation requiring the first polypeptide to retain the ability to bind biotin, this is merely a description of what the fusion protein must be able to do, not what the fusion protein is. Since the specification fails to disclose which amino acids within the amino acid sequence set forth in SEQ ID NO: 2 may be substituted, or by which amino acids these amino acids may be replaced, so that the fusion protein that has an amino acid

sequence that is at least 90% identical to the amino acid sequence of SEQ ID NO: 2 retains the ability to bind biotin, the skilled artisan could not possibly recognize a reasonable number of members of the claimed genus of fusion proteins. Therefore, the disclosure is not sufficiently detailed to reasonably convey to the skilled artisan that Applicants had possession of the claimed invention at the time the application was filed. Accordingly, the rejection of claims 18-22, 38, 39, and 65 under 35 U.S.C. 112, first paragraph for the reasons stated in the Office Action mailed June 22, 2001 (Paper No. 8) is maintained.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the Office Action mailed June 22, 2001 (Paper No. 8).

As stated in the Office Action mailed June 22, 2001, claim 24 is vague and indefinite because the claim recites the phrase "capable of forming a tetrameric complex". The use of the phrase renders the claims vague and indefinite because it is unclear whether the claim requires the fusion protein to actually be able to form a tetrameric complex, and if so, under which conditions, or merely requires the fusion protein to have the potential of doing so. Furthermore, it is also unclear how the claim requires the tetrameric complex to form (e.g., covalently, non-covalently, etc.) and whether the claim requires the interaction between the first fusion protein and the second, third, and fourth fusion proteins to be specific or merely non-specific.

Claim 24 is also indefinite because the claim recites the phrase "a first and a second polypeptide joined end to end". As stated in the Office Action, the use of the phrase renders the claim indefinite because it is unclear whether the terms "first polypeptide" and "second polypeptide" are meant to indicate the amino-terminal

polypeptide and the carboxyl-terminal peptide, respectively, or are merely meant to distinguish one from the other. Furthermore, the fact that the first and second polypeptides are joined end to end is not limiting with regard to the orientation of the polypeptides relative to one another within the fusion protein, so the subject matter encompassed by the claim is not clearly delineated from that which Applicants do not regard as their invention.

Applicants have traversed these grounds of rejection under 35 USC § 112, second paragraph, arguing that the skilled artisan would readily understand the phrase "capable of forming a tetrameric complex". This argument is not persuasive, however. The artisan of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention, since recitation of the phrase renders the claim vague and indefinite for the reasons stated in the Office Action mailed June 22, 2001 and reiterated above, and therefore claim 24 fails to meet the requirements of 35 USC § 112, second paragraph. Amending claim 24 to further recite "similar to that of native streptavidin" after the phrase does not obviate the grounds of rejection, since it is still unclear whether the claim requires the fusion protein to actually be able to form a tetrameric complex, and if so, under which conditions, or merely requires the fusion protein to have the potential of doing so. Also, it is still unclear how the claim requires the tetrameric complex to form (e.g., covalently, non-covalently, etc.) and whether the claim requires the interaction between the first fusion protein and the second, third, and fourth fusion proteins to be specific, or merely non-specific. Furthermore, Applicants' amendment and remarks have not served to clarify whether in claim 24, the terms "first polypeptide" and "second polypeptide" are meant to indicate the amino-terminal polypeptide and the carboxyl-terminal peptide, respectively, or are merely meant to distinguish one from the other. Accordingly, although Applicants' arguments have been carefully considered, these grounds of rejection under 35 USC § 112, first paragraph are maintained.

Claim R jections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 18-39 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dubel, et al (*Journal of Immunological Methods* **178**: 201-209, 1995; Form PTO-1449, Paper No. 6, page 3), as evidenced by Kipriyanov, et al (*Human Antibodies and Hybridomas* **6**: 93-101, 1995; Form PTO-1449, Paper No. 6, page 4), in view of Desplancq, et al (*Protein Engineering* **7**: 1027-1033, 1994; Form PTO-1449, Paper No. 6, page 3), Anderson, et al (*Clinical Immunology and Immunopathology* **84**: 73-84, 1997), McLaughlin, et al (*Oncology* **12**: 1763-1769, 1998), the Internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), Gallizia, et al (*Protein Expression and Purification* **14**: 192-196, 1998; Form PTO-1449, Paper No. 6, page 3), and Pahler, et al (*Journal of Biological Chemistry* **262**: 13933-13937, 1987), Aragarana, et al (*Nucleic Acids Research* **14**: 1871-1882, 1986; Form PTO-1449, Paper No. 6, page 1), Ohno, et al (*DNA and Cell Biology* **15**: 401-406, 1996; Form PTO-1449, Paper No. 6, page 5), and Goshorn, et al (*Cancer Research* **53**: 2123-2127, 1993; Form PTO-1449, Paper No. 6, page 3) for the reasons stated in the Office Action mailed June 22, 2001 (Paper No. 8).

As stated in the Office Action mailed June 22, 2001, Dubel, et al teaches a first fusion protein capable of forming a tetrameric complex with a second, third, and forth fusion protein, wherein the fusion proteins comprise a first polypeptide comprising a portion of streptavidin and a second polypeptide comprising a fragment of an antibody that specifically binds a cell-associated stromal or matrix protein. Dubel, et al disclose that the fusion protein consists of single-chain antibody 215 joined end to end with core-streptavidin by a spacer (i.e., linker) of 5 amino acids (page 203, Figure 1). The variable light and variable heavy chains of the single-chain antibody are connected by a linker of 15 amino acids, as evidenced by Kipriyanov, et al (page 95, Figure 1). The single-chain antibody is derived from a mouse (i.e., murine) antibody, which specifically

binds an epitope of RNA polymerase II, a cell-associated stromal or matrix protein (page 205, column 1). Dubel, et al teach that the fusion protein can form tetrameric complexes and binds antigen (abstract). Furthermore, Dubel, et al teach that "the variable region (Fv) portion of an antibody is comprised of its V_H and V_L domains and is the smallest antibody fragment containing a complete antigen binding site" (page 201, column 2). Dubel, et al teach that single-chain Fv antibodies (scFv) "represent potentially very useful molecules for the targeted delivery of drugs, toxins, or radionuclides to a tumour site" (page 201, column 2). Dubel, et al disclose that "various heterologous protein moieties can also be genetically fused to scFv antibodies to generate bifunctional fusion proteins" (page 202, column 1). Additonally, Dubel, et al teach that streptavidin "exhibits one of the strongest noncovalent binding affinities known for a biomolecule", namely biotin (page 208, column 1). Dubel, et al teach that the fusion protein comprising a single-chain antibody and streptavidin might be "usefully employed for the in vitro purging of autologous bone marrow transplants to eliminate B lymphocytes in the treatment of leukemias and malignant lymphomas" (page 208, column 1).

However, Dubel, et al do not explicitly teach that the first polypeptide of the fusion protein can comprise at least 129 amino acid residues of streptavidin or at least amino acids 14 to 150 of streptavidin, as depicted in Figure 4, or amino acids 38 to 174 of streptavidin, as depicted by SEQ ID NO: 2. Also, Dubel, et al do not explicitly teach that the fusion protein can comprise a linker connecting the first and second polypeptides that consists of between 5 and 10 amino acids. Dubel, et al do not explicitly teach that the antibody from which the fusion protein is derived can be Primatized™. Furthermore, Dubel, et al do not explicitly teach that the antibody from which the fusion protein is derived can bind specifically to CD20 or that the antibody can be produced by the hybridoma cell line B9E9, which produces the monoclonal antibody B9E9 that specifically binds CD20. Finally, Dubel, et al do not explicitly disclose that the linker connecting the variable light and variable heavy chains of the single-chain antibody can comprise at least 20 amino acids, wherein said linker comprises four gly_4ser linkers.

Nonetheless, Kipriyanov, et al teach that the single-chain antibody-streptavidin fusion protein of Dubel, et al was developed "to increase the avidity of single-chain antibodies (scFv) for their antigen" (abstract). Kipriyanov, et al teach that the fact that the single-chain antibody-streptavidin fusion protein can form tetramers and therefore overcomes one limitation of scFv, which due to their monovalency have decreased avidity relevant to polyvalent antibodies (page 93, column 1). Kipriyanov, et al conclude, "the affinity of the scFv-antibody complex was substantially increased by avidity effects due to the tetrameric structure" (abstract). Also, Kipriyanov, et al disclose that "deletions of several amino acids from the N-/C-terminus resulting in a core-streptavidin molecule did not influence the biotin binding" (page 94, column 1).

Ohno, et al teach that tissue-specific delivery of a variety of molecules is a valuable technique for medical research (abstract). Ohno, et al disclose that "the cell-targeting moiety can be either antibodies or protein ligands (growth factors) that recognize the corresponding antigens or receptor (page 401, column 1). Ohno, et al demonstrate that a streptavidin-ligand fusion protein, ST-TGF-α, efficiently targets biotinylated protein to cells that express the ligand's receptor (page 404, Figure 3). Ohno, et al teach that streptavidin-ligand and streptavidin-antibody fusion proteins have a number or advantages over immunotoxins and recombinant toxins for treatment of disease, namely cancer (pages 404-405). "Because biotin can be easily incorporated into a wide range of macromolecules without interfering with biological activities (Wilchek and Bayer, 1990) steptavidin containing-proteins such as ST-TGF-α have wider applicability as bridges to deliver specific molecules such as toxins" (page 405, column 1). Then, Ohno, et al teach that "other chimeric molecules in which the TGF-α moiety has been replaced by an alternate targeting element may have equally broad applicability to targeting a variety of cell types with equal affinities" (page 405, column 2).

Gallizia, et al teaches a method for producing a fusion protein comprising a first and a second polypeptide joined end to end, wherein the one of the two polypeptides comprising said fusion protein comprises at least 129 residues of streptavidin.

Specifically, Gallizia, et al teach that one of the two polypeptides comprising the fusion protein consists of amino acids 15 to 159 of streptavidin (page 193, column 2) while the other polypeptide consists of amino acid sequence that differs by at least one residue from the other polypeptide. Gallizia, et al teach that the fusion protein comprising a portion of streptavidin retains the functional capacity to bind iminobiotin (page 196, column 1).

Pahler, et al teach that streptavidin is "known to be susceptible to proteolysis near the N terminus" (page 13934, column 1). Pahler, et al teach that streptavidin is cleaved at or near residue 14, close to the amino-terminus, within its amino acid sequence (page 13394, Figure 1). Pahler, et al also teach that the carboxyl-terminal of streptavidin is susceptible to protease activity (page 13934, column 1). Also, Pahler, et al teach that "core streptavidin", which has been proteolytically truncated at both ends, retains its ability to bind biotin (abstract).

Desplancq, et al teach that "thirteen scFv variants with linkers comprising up to six repeats of the motif Gly-Gly-Gly-Gly-Ser were studied" (abstract). Desplancq, et al disclose that "the V_L-linker-V_H variant with a 30 amino acid linker showed slightly poorer binding activity than the monovalent F(ab') standard" (page 1030, column 2). Desplancq, et al teach that "precipitation problems can be overcome by utilizing loner linkers" (page 1033, column 1). Desplancq, et al also teach that single-chain Fv antibodies "are of interest for clinical applications because their pharmacokinetics and biodistribution may be superior to those of whole antibodies in some clinical applications" (page 1027, column 1).

Goshorn, et al teach the production and use of a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first and second polypeptides are joined end to end, but separated by a linker of 6 amino acids, wherein one of the polypeptides is a single-chain antibody (page 2124, Figure 1). Goshorn, et al teach that the fusion protein is able to bind specifically to tumor cells displaying the antigen to which the antibody from which the fusion protein is derived binds (page 2126, Figure 3). Goshorn, et al also teach that the second polypeptide of which the fusion protein is comprised retains its capacity to bind substrate (page 2126, Figure 4). Furthermore,

Goshorn, et al teach that "a promising new approach for tumor therapy is to use the antigen-binding capability of an antibody to deliver enzymatic activities to tumor tissues, which are then exploited to convert relatively nontoxic prodrugs into more active chemotherapeutic agents" (page 2123, column 1).

Anderson, et al teach the production and use of a Primatized™ monoclonal antibody (abstract). Anderson, et al teach that the use of Primatized™ monoclonal antibodies circumvents the problems associated with administration of xenogeneic monoclonal antibodies to treat human diseases, such a anti-mouse human immune response, which limits the applicability and efficacy of pharmaceutical compositions comprising mouse monoclonal antibodies (page 74, column 1).

McLaughlin, et al teach the clinical status and optimal use of Rituximab™, a recombinant humanized monoclonal antibody that specifically binds CD20 (abstract). Mclaughlin, et al disclose that "as the first MoAb [monoclonal antibody] to gain FDA approval for the treatment of a malignancy, rituximab signals the beginning of a promising new era in cancer therapy" (abstract).

The Bioprobe BV catalog demonstrates that the hybridoma that produces the anti-CD20 monoclonal antibody B9E9 is commercially available (page 5 of the Internet published catalog).

Therefore, as stated in the Office Action mailed June 22, 2001, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dubel, et al to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises at least 129 amino acid residues of streptavidin or at least amino acids 14 to 150 of streptavidin, because Arragarana, et al teach that the first 24 amino-terminal amino acids compose a signal sequence that is cleaved and because Pahler, et al teach that about the next 13 amino acids of streptavidin are susceptible to protease cleavage. Therefore, if one of ordinary skill in the art were to be motivated to produce a fusion protein comprising an amino-terminal first polypeptide, wherein the first polypeptide is a fragment of streptavidin, it would have been obvious, in light of the teachings of Pahler,

et al, to truncate the amino-terminus of streptavidin, in order to decrease the susceptibility of the free amino-terminus to protease activity while retaining as much of the structure of streptavidin as possible to insure the maintenance of its biotin-binding capacity. Additionally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dubel, et al to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first and second polypeptides are separated by a linker that is between five and ten amino acids, because Goshorn, et al teach that a fusion protein comprising a first and a second polypeptide can be produced, wherein the first and second polypeptides are separated by a linker of 6 amino acids, which retains the ability to bind specifically to the antigen to which the antibody from the which the fusion protein is derived binds and which retains the ability to bind specifically to the substrate to which the second polypeptide from which the fusion protein is derived binds. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the teachings of Dubel, et al to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide is an antigen-binding fragment of the monoclonal antibody B9E9, because monoclonal antibody B9E9 specifically binds CD20 and is commercially available and easily obtained. One of ordinary skill in the art would appreciate the fact that, based upon the teachings of Dubel, et al, the fusion of an antigen-binding fragment of the monoclonal antibody B9E9 and a second polypeptide could be used to selectively and specifically target the second polypeptide, which is fused to the first polypeptide, to a CD20+ lymphoma tumor cell, because McLaughlin, et al teach that anti-CD20 antibody-directed therapy can be used effectively to treat patients diagnosed with lymphoma. In light of the teachings of Dubel, et al Desplancq, et al, and Goshorn, et al, for example, the selectivity and binding specificity of monoclonal antibodies and antigen-binding fragments thereof was well known in the art at the time the invention was made. Because the second polypeptide of Dubel, et al is a biotin-binding fragment of streptavidin, one of ordinary skill in the art would appreciate the fact that the fusion protein could be used to selectively target biotinylated-chemotherapeutic agents to CD20+ cells bound specifically by the antibody

portion of the fusion protein, because according to Dubel, et al, streptavidin has a very high affinity for biotin. Because Dubel, et al teach that the fusion protein forms tetramers, one of ordinary skill in the art would appreciate the fact that four biotinylated molecules could potentially be targeted to the CD20+ lymphoma tumor cells. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a fusion protein, according to the methodology of Dubel, et al, comprising a single-chain Fv derived from the monoclonal antibody B9E9, because Dubel, et al teaches that scFv are the smallest fragments of an antibody to retain specific antigen-binding capacity and therefore, as Desplanqc, et al teach, the pharmacokinetics and biodistribution of scFv may be superior to those of whole antibodies. In light of the teachings of Anderson, et al, it also would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the teachings of Dubel, et al to produce a fusion protein comprising a single-chain Fv derived from a recombinant Primatized™ or humanized antibody derived from the mouse monoclonal antibody B9E9, because Anderson, et al teaches that Primatized™ antibodies overcome limitations caused by the immunogenicity of xenogeneic antibodies formulated as pharmaceutical compositions for use in humans. Finally, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the fusion protein of Dubel, et al to separate the variable and heavy chains of the scFv antibody component of the fusion protein, because Desplanqc, et al teach that a scFv antibody consisting of variable heavy and light chains separated by a linker of at least 20 amino acids, wherein the linker consists of at least four gly_4-ser motifs, maintains antigen-binding specificity and because Desplanqc, et al teach that the use of a longer linker may overcome problems that occur during production of the single-chain antibodies.

One of ordinary skill in the art would have been motivated to modify the fusion protein of Dubel, et al, according to the teachings of McLaughlin, et al, Anderson, et al, and Desplanqc, et al, to produce a recombinant Primatized™ single-chain anti-CD20 B9E9 antibody-streptavidin fusion protein, because there is a long-felt need for a more

effective therapy for lymphoma, because the hybridoma producing the recombinant antibody B9E9 is commercially available and would be required to produce the recombinant antibody-streptavidin fusion protein, and also because Dubel, et al teach that single-chain antibody-streptavidin fusion proteins can be used to treat lymphoma, McLaughlin, et al teach that anti-CD20 antibody therapy can be used effectively treat lymphoma, Desplancq, et al teach the advantages of using scFv antibodies, and Anderson, et al teach the advantages of using Primatized™ antibodies in treating humans. One of ordinary skill in the art would have been motivated at the time the invention was made to construct an expression cassette encoding a fusion protein comprising at least 129 amino acids of streptavidin, including at least amino acids 14-150, because the first 24 amino-terminal amino acids of the translation product compose a signal sequence that is cleaved, according to the teachings of Aragarana, et al, and also because the further truncation of the amino-terminus or carboxyl-terminus of the streptavidin portion of the fusion protein would limit the fusion protein's susceptibility to protease activity without effecting its biotin-binding capacity, according to the teachings of Pahler, et al. Also, one of ordinary skill in the art would have been motivated at the time the invention was made to separate the first and second polypeptides of the fusion protein, namely streptavidin and the single-chain antibody, because the insertion of a linker would facilitate insertion of a multiple cloning site into vector encoding the fusion protein so that the segment of the vector encoding the single-chain antibody can be easily replaced by another segment encoding a different single-chain antibody. Finally, one of ordinary skill in the art would have been motivated at the time the invention was made to separate the variable heavy and light chains of the single-chain Fv antibody by a linker consisting of four gly-gly-gly-gly-ser linkers, because Desplancq, et al teach that problems with precipitation that are encountered during the manufacture of recombinant antibodies might be overcome by the use of a longer linker separating the variable heavy and light chains of the scFv antibody.

Applicants have traversed the rejection of the claims under 35 USC § 103(a), arguing:

(a) The cited references, either alone or in combination, do not teach or suggest all elements of the claimed invention. In particular, Applicants contend that none of the references cited as a part of the basis of the rejection, and specifically not Dubel, et al, teach or suggest "a genomic streptavidin expressed gene fusion, comprising at least 129 amino acids of streptavidin [...] or at least amino acids 14-150 of streptavidin" (page 15, paragraph 3).

(b) The invention is "non-obvious in light of the prior art's use of fusion proteins comprising core streptavidin, amino acids 14-136" (page 15, paragraph 4). Applicants also submit that the invention has a substantial and heretofore unrecognized advantage over core streptavidin fusion proteins, which discovery Applicants contend was surprising in light of the prior art, and "[s]uch unexpected findings clearly render the presently claimed invention non-obvious in light of Dubel, et al., or any of the cited prior art references" (page 16, paragraph 1).

In reply to Applicants' arguments, first, it is noted that the claims are rejected under 35 USC § 103(a) in as being unpatentable over Dubel, et al, as evidenced by Kipriyanov, et al, in view of Desplancq, et al, Anderson, et al, McLaughlin, et al, the Internet edition of the Bioprobe BV Catalog of Mouse Hybridomas (Bandung, Indonesia), Gallizia, et al, Pahler, et al, Aragarana, et al, Ohno, et al, and Goshorn, et al. Accordingly, the answer to Applicants apparent query in their remark that the cited references, either alone or in combination, do not teach or suggest all elements of the claimed invention, is that the invention is unpatentable over the *combination* of the teachings of the cited references. In this regard, it is noted that Applicant addressed some of the cited references individually, but one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Furthermore, as stated in the rejection, although Dubel, et al do not explicitly teach that the first polypeptide of the fusion protein can comprise at least 129 amino acid residues of streptavidin or at least amino acids 14 to 150 of streptavidin, as depicted in Figure 4, or amino acids 38 to 174 of streptavidin, as depicted by SEQ ID

NO: 2, Gallizia, et al teach that one of the two polypeptides comprising a fusion protein consists of amino acids 15 to 159 of streptavidin and that the fusion protein comprising this portion of streptavidin retains the functional capacity to bind biotin. Since obviously a fusion protein comprising amino acids 15 to 159 of streptavidin also comprises at least 129 amino acids of streptavidin, it is apparent that Gallizia, et al is anticipatory of the claimed invention, at least in part, and accordingly Gallizia, et al should have been used as the basis of a rejection of the some of the claims under 35 USC § 102(b). Nevertheless, as also stated in the rejection of the claims under 35 USC § 103(a), because Arragarana, et al teach that the first 24 amino-terminal amino acids compose a signal sequence that is cleaved and because Pahler, et al teach that about the next 13 amino acids of streptavidin are susceptible to protease cleavage, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dubel, et al to produce and use a fusion protein comprising a first polypeptide and a second polypeptide, wherein the first polypeptide comprises at least 129 amino acid residues of streptavidin or at least amino acids 14 to 150 of streptavidin. Applicants are reminded that the test for obviousness is not whether the features of the secondary references may be bodily incorporated into the structure of the primary references; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Although Applicants argue that unexpected findings clearly render the presently claimed invention non-obvious in light of Dubel, et al., or any of the cited prior art references, the fact that Applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Additionally, the Examiner recognizes that combining or modifying the teachings of the prior art to produce the claimed invention can establish the obviousness of a claimed invention only where there is some teaching, suggestion, or motivation to do so found either in the references themselves

or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as stated in the rejection, one of ordinary skill in the art would have been motivated at the time the invention was made to construct an expression cassette encoding a fusion protein comprising at least 129 amino acids of streptavidin, including at least amino acids 14-150, because the first 24 amino-terminal amino acids of the translation product compose a signal sequence that is cleaved, according to the teachings of Aragarana, et al, and also because the further truncation of the amino-terminus or carboxyl-terminus of the streptavidin portion of the fusion protein would limit the fusion protein's susceptibility to protease activity without effecting its biotin-binding capacity, according to the teachings of Pahler, et al.

In summary, Applicants' arguments have been carefully considered but have not been found persuasive. Therefore, the rejection of claims 18-39 and 65 under 35 U.S.C. 103(a) as being unpatentable over Dubel, et al, as evidenced by Kipriyanov, et al, in view of Desplancq, et al, Anderson, et al, McLaughlin, et al, the Internet edition of the Bioprobe BV Catalog of Mouse Hybridomas, Gallizia, et al, Pahler, et al, Aragarana, et al, Ohno, et al, and Goshorn, et al for the reasons stated in the Office Action mailed June 22, 2001 (Paper No. 8) is maintained.

New Grounds of Claim Rejections

Claim Rejections – 35 USC § 112

15. Claims 18-39 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the single-chain antibody-streptavidin fusion proteins huNR-LU-10 scFvSA and B9E9 scFvSA, does not reasonably provide enablement for any other fusion protein comprising a first polypeptide comprising a functional variant of streptavidin that retains the ability to bind biotin and has an amino acid sequence that is at least 90% identical to the amino acid sequence of native streptavidin, as set forth in SEQ ID NO: 2, or for any pharmaceutical composition comprising such a fusion protein. The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification is not reasonably commensurate in scope with the claims. Moreover, given only the benefit of the disclosure, the skilled artisan could not make and use the claimed invention with a reasonable expectation of success without the need to perform additional undue experimentation.

The art of protein chemistry and protein engineering is highly unpredictable. Although the claims encompass fusion proteins comprising a first polypeptide that has an amino acid sequence that differs from the amino acid sequence of SEQ ID NO: 2 and still retains the ability to bind biotin, the specification does not teach a method for making or using such fusion proteins. In particular, the specification fails to teach which amino acids of the amino acid sequence set forth in SEQ ID NO: 2 can be replaced, and by which amino acids the replacements can be made, without adversely affecting the ability of the fusion protein to bind biotin. The skilled artisan cannot predict which amino acids might be replaced, or by which amino acids such replacements might be made, because the art is so highly unpredictable. Therefore, the skilled artisan cannot make and use the claimed invention with a reasonable expectation of success without need to first perform additional and undue experimentation.

With each and every discrepant nucleotide residue, the predictability that the claimed fusion protein will function similarly enough to the native streptavidin for this instant disclosure to considered enabling declines significantly. In fact, even a single nucleotide alteration in the amino acid sequence of a protein can drastically alter the function of the protein. Bowie, et al (*Science* **257**: 1306-1310, 1990) teach that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Even if the skilled artisan were able to submit a complete list of the possible fusion proteins, which might fall within the scope of the claims, the skilled artisan could not

predict which of these would function similarly to native streptavidin to be encompassed by the claims and to have the asserted utility of the claimed invention, and which would not, because Bowie, et al teach that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Bowie, et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). Because the specification fails to provide essential guidance and direction and because the art is so highly unpredictable, the skilled artisan would only be able to empirically determine whether fusion proteins have similar or identical function to native streptavidin, and therefore, the skilled artisan could not make or use the invention with a reasonable expectation of success without first having to perform undue experimentation.

In further support of the high degree of unpredictability and the consequent need to perform undue experimentation to make and use the claimed invention with a reasonable expectation of success in the absence of a sufficient disclosure, which includes working exemplification, guidance, and direction that is reasonably commensurate in scope with the claims, Burgess, et al (*Journal of Cell Biology* **111**: 2129-2138, 1990) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess, et al teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example, Lazar et al (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, as evident from the teaching

of Lazar, et al, even a *single conservative* type amino acid substitution may adversely affect the function of a protein.

Considering the teachings of the references cited above, it is apparent that even a single amino acid substitution can dramatically affect the biological activity and the structure-function characteristics of a protein. Therefore, in summary, the specification fails to meet the enablement requirement of 35 USC § 112, first paragraph because the disclosed teachings, guidance, direction, and exemplification is not reasonably commensurate in scope with the claims and one skilled in the art could not make and use the claimed invention with a reasonable expectation of success without first having to perform undue experimentation.

16. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is vague and indefinite because the claim recites the phrase "a tetrameric complex similar to that of native streptavidin". Recitation of the phrase renders the claim vague and indefinite because it cannot be ascertained to how, or to what extent the claim requires the tetrameric complex formed to be similar to native streptavidin (or even to a tetrameric complex composed of native streptavidin). Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Conclusion

17. No claims are allowed.

18. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached at (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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slr
May 14, 2002